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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,422	03/27/2006	Birke Bartosch	P08575US00/BAS	4780

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,422	BARTOSCH ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-91* is/are pending in the application.

4a) Of the above claim(s) *57,67,71-81 and 88-90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-56,58-66,68-70,82-87 and 91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-45 have been cancelled. Claims 57, 67, 71-81 and 88-90 have been withdrawn. Claims 54 and 70 have been amended. Claim 91 is new.

Claims 46-56, 58-66, 68-70, 82-87, and 91 are under examination.

2. The provisional nonstatutory obviousness-type double patenting rejection of claims 46-56, 58-66, 68-70, and 82-87 as being unpatentable over claims 1-8, 10-16, 18, 27, 28, and 30 of copending Application No. 10/547,750, in view of Lechmann et al. (Hepatology, 2001, 34: 4117-423) is withdrawn because Applicant submitted a terminal disclaimer on 03/02/2009.

The rejections of claims 54 and 70 under 35 U.S.C. 112, second paragraph, as being indefinite, are withdrawn in response to Applicant's amendments to the claims filed on 03/02/2009.

Response to Arguments

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 46-56, 58-66, 68-70, and 82-87 remain, and claim 91 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco et al. (WO 00/55335), in view of both Lechmann et al. (Hepatology, 2001, 34: 4117-423) and Ray et al. (FEMS Microbiology Letters, 2001, 202: 149-156).

Marasco et al. teach an *ex vivo* method of producing infectious virus-like particles such as a flavivirus-like particle by **(i)** providing a packaging retroviral vector comprising a transgene and the cis-acting elements necessary for encapsidation, reverse transcription, and integration (i.e., a first nucleic acid sequence comprising a packaging competent retroviral genome), a vector encoding the retroviral gag-pol (i.e., a second vector comprising a cDNA encoding retroviral the core proteins), and a vector encoding the flavivirus envelope proteins (i.e., a third nucleic acid sequence comprising a cDNA encoding the envelope proteins), and **(ii)** transfecting host cells with the vectors above, culturing the transfected host cells to express the viral proteins and form the viral particles (claims 46, 48, 58, 70, and 84) (p. 4, third full paragraph, p. 6, first and second full paragraphs, p. 7, first paragraph, p. 16, p. 12, first and third paragraphs, p. 34, last paragraph, p. 41, third and fourth full paragraphs, claims 1-3 and 6-12). Marasco et al. also teach purifying their viral particles and using them to induce immune responses or to deliver transgenes to cells (claims 59, 82, and 83) (p. 34, last paragraph, p. 35). Although Marasco et al. teach their method as suitable to make infectious flavivirus-like particles, they do not specifically teach HCV, nor do they teach a HCV polyprotein comprising in order the core protein, the native E1 and E2 proteins, and the native p7 protein (claims 46-56, 58-66, 68-70, 82-87, and 91). Lechmann et al. teach obtaining

infectious HCV-like particles wherein the HCV-like particles are made by using a vector encoding a polyprotein comprising successively the HCV core, E1, E2 and p7 proteins (Abstract, p. 417, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Marasco et al. by using the polyprotein of Lechmann et al. to achieve the predictable result of obtaining infectious HCV-like particles. By including HCV core protein, one of skill in the art would have necessarily included a signal sequence because the HCV core protein comprises a signal sequence, wherein the signal sequence is required for the proper polyprotein targeting to the host cell endoplasmic reticulum (see Ray et al., p. 150, column 1 and Fig. 1). With respect to the limitation of a signal peptide derived from a type I membrane protein (claims 46 and 70), it is noted that the instant claim 70 defines that the signal sequence from a type I membrane protein could be the signal sequence from the core protein. Therefore, the combined teachings of Marasco et al. and Lechmann et al. disclose an infectious HCV-like particle obtained by using a nucleic acid sequence comprising a cDNA encoding a polyprotein containing successively a signal peptide from a type I protein, and the HCV E1, E2, and p7 proteins. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection grounds that, in contrast to the present application, Marasco et al. describe a system of vectors that are useful for gene delivery and comprise a first vector that includes a lentiviral gag gene encoding a lentiviral gag protein, a second vector that includes an env gene encoding a functional envelope

protein, a lentiviral pol gene encoding a lentiviral pol protein, and a packaging vector that contains a nucleic acid encoding a desired molecule. Marasco et al. specify that the env gene may be heterologous and may be from a virus of the hepatitis or the flavivirus group. However, Marasco et al. only cite the HAV, HBV, and HEV viruses as sources of an env gene, and do not teach or suggest that HCV could be utilized. Applicant also argues that, the information disclosed in Marasco et al. and Lechmann et al. would not have led one of ordinary skill in the art to utilize HCV proteins to obtain infectious HCV-like particles, as described in the present application. Marasco et al. describes numerous associations between cell lines and particular virus types, including HAV, HBV, HEV, and flavivirus. However, hepacivirus and HCV are expressly excluded from the exhaustive list of viruses described by Marasco et al., which would lead one of ordinary skill in the art to conclude that the methods described in Marasco would not be applicable to HCV or hepaciviruses. Although all hepatitis viruses infect hepatocytes and cause hepatitis, each hepatitis virus is distinct genetically and clinically. As such, the use of the other hepatitis viruses, namely HAV, HBV, and HEV, in the methods of Marasco et al. do not teach or in any way suggest that HCV could also be used in the methods described by Marasco et al. Furthermore, Lechmann et al. provide no teaching or suggestion that a polyprotein comprising HCV core, E1, and E2 proteins could be used in the method of Marasco et al. to obtain infectious HCV-like particles. Indeed, Lechmann et al. do not teach or suggest that the HCV-like particles described in that reference are immunogenic, much less teach or suggest that these pseudoparticles are infectious, and thus capable of initiating an infection and/or cell entry. Ray et al. add

nothing further in this regard and was merely cited by the Examiner for its teachings regarding the signal sequence of the HCV core protein. Accordingly, Applicant submits that the present invention is not rendered obvious by the Marasco et al., Lechmann et al., or Ray et al. and that the claims of the present application relating to a method for producing infectious hepacivirus-like particles are clearly patentable over those references. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For this reasons, Applicant's arguments that Marasco et al. do not teach or suggest that HCV is irrelevant to the instant rejection. None of the cited references has to teach each and every claim limitation. If they did, this would have been anticipation and not an obviousness-type rejection. Applicant argues that hepaciviruses and HCV are expressly excluded from the exhaustive list of viruses described by Marasco et al. In response to this argument, it is noted that just because they do not mention it, does not mean that Marasco et al. expressly exclude hepaciviruses and HCV. There is no teaching in Marasco et al. indicating that retroviruses cannot be pseudotyped with hepaciviruses or HCV envelope proteins. Certainly, by reading Marasco et al., one of skill in the art would not conclude that their method would not be applicable to HCV or

hepaciviruses. Applicant argues that Lechmann et al. do not teach or suggest that a polyprotein comprising HCV core, E1, and E2 proteins could be used in the method of Marasco et al. to obtain infectious HCV-like particles. This is just an argument not supported by any evidence. Obtaining pseudotyped viruses (including retroviruses) was routine in the prior art. The argument that each hepatitis virus is genetically and clinically distinct is not found persuasive. Viruses are routinely pseudotyped with envelope proteins obtained from unrelated viruses. Applicant did not provide any evidence indicating that one of skill in the art could not have been successful in pseudotyping retroviruses with HCV core, E1, and E2. In fact, there is no such evidence in the art. Applicant argues that Lechmann et al. do not teach or suggest that the HCV-like particles described in that reference are immunogenic or infectious. In response to this argument, it is noted that Lechmann et al. do teach their particles as being immunogenic (Abstract). With respect to infectivity, Lechmann et al. do not have to teach or suggest such. An obviousness-type rejection is based on the knowledge in the prior art as a whole. Motivation to combine can be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the prior art teaches that viruses pseudotyped with HCV core, E1, and E2 are infectious and immunogenic (see Ezelle et al., J. Virol., 2000, 76: 12325-12334, Abstract, p. 12327, column 2, p. 12328, column 2). Based on the teachings in the prior art as a whole, one of skill in the art would have reasonably expected to be successful to obtain infectious and immunogenic

hepacivirus-like particles by pseutotyping retroviruses with the HCV core, E1, and E2. For these reasons, Applicant's arguments are not found persuasive and the rejection is maintained.

Conclusion

5. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ezelle et al., J. Virol., 2000, 76: 12325-12334 was cited in response to Applicant's argument that that Lechmann et al. do not teach or suggest that the HCV-like particles described in that reference are immunogenic or infectious. Specifically, the reference teaches that viruses pseudotyped with HCV core, E1, and E2 are infectious and immunogenic.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633